REMARKS

After entry of the above amendments and new claim 20, claims 1-3, 5, 8-13 and 16-20 are pending and stand rejected, claims 6, 7, 14 and 15 have been withdrawn from consideration, and claim 4 has been canceled. The above claim amendments add no new matter. Support for the amendment to claim 3 can be found at page 16, lines 29-35. Support for the amendments to claims 18 and 19 can be found throughout the application, *e.g.* at page 35, line 4 to page 36, line 26. Support for new claim 20 can be found at page 17, lines 4-17. In addition, the above amendments to the specification also introduce no new matter and are provided to correct certain obvious typographical errors.

Obviousness-Type Double Patenting

The Office Action states that claims 18 and 19 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-22 of U.S. Patent 6,372,427. Applicants respectfully traverse this rejection, because the claimed invention, as reflected in amended claims 18 and 19, is not obvious over claims 1-7 and 15-22 of the '427 patent.

First, Applicants note that amended claims 18 and 19 are not anticipated by claims 1-7 and 15-22 of the '427 patent because the claims do not provide every element of the claimed invention. In particular, claims 1-7 and 15-22 of the '427 patent do not provide "a pharmaceutically acceptable carrier" as required by amended claims 18 and 19. Accordingly, amended claims 18 and 19 are not subject to obviousness-type double patenting as being anticipated by claims 1-7 and 15-22 of the '427 patent.

Second, amended claims 18 and 19 are not obvious in view of claims 1-7 and 15-22 of the '427 patent. In obviousness-type double patenting, only the claims of the issued patent may be considered as prior art (see M.P.E.P. §804, paragraph II.B.1). The specification is to be used only as a dictionary in determining the meaning of terms of the claimed invention (see M.P.E.P. §804, paragraph II.B.1, citing In Re Boylan, 392 F.2d 1017 (CCPA 1968)). Claims 1-7 and 15-22 of the '427 patent are drawn to a composition, and the specification provides guidance as to the meaning and possible uses of the claimed "composition." In particular, the '427 patent notes

the use of the claimed composition for: "HIV-1 virus inhibition properties in cell cultures" (column 12, lines 1-3); its "[Use] to identify the presence of the nucleic acids of a particular virion or bacteria in cell cultures . . ." (column 13, lines 3-8), and its "[Use in examining] the function of various genes in an animal . . ." (column 13, lines 9-18). Applicants respectfully note that each of these uses is neither pharmaceutical in nature, nor specifically requires a pharmaceutically acceptable carrier. Accordingly, the instantly claimed pharmaceutical compositions incorporating a "pharmaceutically acceptable carrier," are not obvious in view of the claimed composition having numerous non-pharmaceutical applications.

Furthermore, nothing in claims 1-7 and 15-22 of the '427 patent suggests the "pharmaceutical composition comprising a pharmaceutically acceptable carrier" of amended claims 18 and 19, because these issued claims of the '427 patent simply do not render obvious the additional claimed element, or any other suitable modifications, to achieve the claimed "pharmaceutical composition". The obviousness-type double patenting rejection is therefore improper because of this lack of suggestion in the prior art claims. See In Re Baird, 16 F.3d 380, 382 (Fed. Cir. 1994) (holding fact that claimed compound may be encompassed by a disclosed generic formula does not itself render that compound obvious); In Re Jones, 958 F.2d 347, 351 (Fed. Cir. 1992) (refusing to hold that broad disclosure of chemical genus renders obvious any species that happens to fall within it).

Accordingly, in view of the amendments to claims 18 and 19 and the above-presented arguments, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §103

The Office Action states that claims 1-6, 8-13, and 17 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Gryaznov *et al.* (U.S. Patent No. 5,571,903) (the '903 patent) in view of Agrawal *et al.* (U.S. Patent No. 5,691,316) (the '316 patent). In particular, the Office Action states that it would have been obvious at the time the invention was made to modify the oligonucleotides of the '903 patent with the cyclodextrin or adamantane / cyclodextrin moieties of the '316 patent. Applicants respectfully traverse this rejection for the reasons that follow.

First, Applicants respectfully note that the '903 patent describes complexes that form only after the individual oligonucleotides have annealed to their targets utilizing nonspecific, low affinity interacting moieties such as lipophilic groups (*e.g.* fatty acids, waxes, or steroids) ("[C]ombinations of two or more oligonucleotides or analogs thereof that are capable of stable complexes when annealed . . .", col. 1, line 8; "Whenever the oligonucleotide moieties specifically anneal to a target . . . terminal binding moieties are capable of spontaneously interacting .. . .", col. 3, lines 5-10; "[U]pon annealing of the oligonucleotide moieties to a target polynucleotide, the terminal binding moieties of each pair are brought into juxtaposition so that they form a stable covalent linkage . . . .", col. 3, line 24).

In contrast, the instant invention requires the presence of a pair of highly specific, high-affinity binding partners which enable the oligonucleotides to form a complex independent of, and prior to, annealing to a target nucleic acid. ("The non-nucleotidic binding partners interact with each other to form complexes.", page 5, lines 22-24; "[T]he invention provides a dimeric structure . . . The first oligonucleotide in the dimer has a terminal non-nucleotidic binding partner which is bound to the non-nucleotidic binding partner of the second oligonucleotide.", page 6, lines 6-16; "The binding partners interact with each other to enable the formation of a dimer (FIG. 1D).", page 14, lines 17-18; "Thus, contact is maintained through the interaction of the linked binding partners . . . .", page 23, lines 3-4). Nothing in the '903 patent would teach or suggest that a high-affinity, high-specificity binding pair such as adamantine-cyclodextrin or biotin-streptavidin, could be substituted for the low-affinity, low-specificity terminal binding moieties of the invention while retaining their intended function of forming a "juxtaposed" antisense complex with an mRNA target. Indeed, many such high affinity binding moieties, including adamantine-cyclodextrin and biotin-streptavidin, were known in the art at the time of the '903 filing but were not taught or suggested in that patent. Nothing in the teachings of the '903 patent alone, or in combination with the teachings of the '316 patent addressed below, would have led the skilled artisan to make such a substitution while maintaining a reasonable expectation of success in the resulting combination.

Further to this point, Applicants note that the instant claimed invention provides a critically advantageous feature not taught or suggested in the '903 patent. This feature provides a major distinguishing feature over the teachings of the '903 patent. In particular, the instant

invention provides for the specific formation of heterodimeric cooperative oligonucleotides that can productively bind to adjacent tandem portions of a target mRNA while avoiding the formation of homodimeric complexes that cannot bind adjacently to the target mRNA. In particular, the '903 patent describes the use of a broad range of lipophilic groups as binding partners. This broad description, as well as the cholesterol-cholesterol binding partner pair example provided (the only hydrophobic complex example provided in the '903 patent) relies upon the non-specific interaction between lipophilic groups, in an aqueous environment, in order to form a low-affinity hydrophobic complex (col. 6, lines 4-10). This nonspecific association between lipophilic groups does not help to ensure the proper linking of appropriately complementary adjacent oligonucleotide pairs because the association does not distinguish between the oligonucleotide moieties.

In contrast, the claimed invention utilizes the highly specific, high-affinity interaction between cyclodextrin and adamantine, or that between biotin and streptavidin, to form specific, stable complexes (page 5, lines 14-28). The high affinity binding partners of the claimed invention facilitate the proper linking of the appropriate adjacently-hybridizing oligonucleotide pairs because the highly specific interaction occurs only between heterodimeric, *e.g.,* between adamantine-linked and cyclodextrin-linked, oligonucleotides and not between homodimeric, *e.g.*, two adamantine-linked, oligonucleotides. Accordingly, the instantly claimed invention, which involves the use of particular high-specificity, high-affinity binding pairs, provides a significant new feature not taught or suggested by the '903 patent. The instant invention is, accordingly, not obvious in view of this art.

Second, the above-cited deficiencies in the teachings of the '903 patent are not cured by the teaching of the second reference cited, U.S. Patent No. 5,691,316 (the '316 patent). The '316 patent does not even teach or suggests a biotin-streptavidin binding pair, a critical feature of one embodiment of the invention, nor does it teach or suggest that a cyclodextin-adamantane binding pair could be used to promote dimerization of adjacently-complementary oligonucleotides, a critical feature of another embodiment of the invention. The '316 patent teaches oligonucleotides that are covalently linked to adamantane alone. The '316 patent does not teach or suggest an oligonucleotide that is covalently linked to cyclodextrin, a critical feature of one embodiment of the invention. Indeed the '316 patent specifically teaches that cyclodextrin is to

be complexed with the subject oligonucleotides noncovalently (*e.g.*, through a covalently-linked admantane moiety) to obtain the desired effects. The '316 patent addresses enhancing cellular uptake and intracellular concentration of an antisense oligonucleotide using noncovalently-associated cyclodextrin. Nothing in the teachings of the '316 patent would lead the skilled artisan to believe that a covalent association of cyclodextrin with an oligonucleotide would provide these desired effects. Accordingly, counter to what is put forth in the Office Action, the '316 patent's teachings would not have motivated the skilled artisan to modify the oligonucleotides taught in the '903 patent with the adamantane/cyclodextrin binding pairs taught in the '316 patent because the teachings of the '316 patent provide that the cyclodextrin must be noncovalently associated with the subject oligonucleotide to obtain the desired enhance cellular uptake and intracellular concentration effects.

Even if the skilled artisan were to consider substituting the covalently-bound cyclodextrin of the instant invention for the non-covalently bound cyclodextrin taught by the '316 patent, they still would not arrive at the claimed invention, because the second non-overlapping and adjacently-hybridizing oligonucleotide of the claimed invention would be lacking. In particular, Applicants respectfully note that the '316 patent teaches the use of a cyclodextrin noncovalently associated with an adamantane, which in turn is covalently bonded to an oligonucleotide, to improve cellular uptake. Thus, the association between cyclodextrin and adamantane in the '316 patent is only for the purpose of creating a cyclodextrin-oligonucleotide complex of a single oligonucleotide. Accordingly, the '316 patent does not suggest to one skilled in the art the use of the cyclodextrin-adamantane complex for the purpose of creating a multi-oligonucleotide complex as the instant application teaches.

Finally, in addition to failing to render obvious the adamantine/cyclodextrin binding pair based embodiments of the instant claimed invention, Applicants further note that the '906 and '316 patents fail entirely to teach or suggest a biotin-streptavidin binding pair. The '906 and '316 patents therefore fail to teach or suggest the biotin-streptavidin based embodiments of the instantly claimed invention. In particular, the skilled artisan would not have substituted biotin-streptavidin binding pairs for the adamantine-cyclodextrin binding pairs taught in the '316 patent, because there would have been no reasonable expectation that the resulting substitution would enhance cellular uptake or intracellular concentration of the subject oligonucleotide.

Similarly, substitution of the hydrophobic binding pairs taught in the '906 patent with biotin-streptavidin binding pairs of the instant invention would not have had a reasonable expectation of success for the reasons presented previously.

Accordingly, the cited combination of art fails to render obvious the full scope of the claimed invention. Accordingly, and for all of the reasons addressed above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

Rejection under 35 U.S.C. §112 (second paragraph)

The Office Action states that claim 3 was rejected as being vague and indefinite for failing to particularly point out and distinctly claim the invention. In particular, the Office Action states that recitation of the phrase "wherein at least one of the oligonucleotides is modified" is vague and indefinite since it is clear that both the first and the second oligonucleotides of the invention are modified to the extent that they encompass oligonucleotides that are linked to a binding partner.

Accordingly, Applicants have amended claim 3, and canceled claim 4, to clarify that the recited modification is "a synthetic linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide." Support for the amendment to claim 3 can be found at page 16, lines 29-35. In addition, Applicants have added new claim 20, which depends from currently amended claim 3, and which further serves to define the scope of the claimed invention to include various specific classes of internucleotidal chemical linkages. Support for new claim 20 can be found at page 17, lines 4-17. In view of these clarifying amendments and new claim 20, reconsideration and withdrawal of the rejection is therefore respectfully requested.

Rejection under 35 U.S.C. §112 (first paragraph)

The Office Action states that claims 16-19 have been rejected under 35 U.S.C. §112, first paragraph, because "the specification while being enabling for using the claimed pharmaceutical formulations and compositions *in vitro*, does not reasonably provide enablement for the *in vivo* use of the claimed formulations or compositions for treatment purposes. Applicants respectfully traverse this rejection for the reasons that follow.

First, Applicants note that the numerous isolated quotations provided in the Office Action in support for this rejection apply only to monomolecular antisense compositions and not to the dimeric antisense complexes, comprising two synthetic oligonucleotides, of the instant invention. Accordingly, it is respectfully suggested that consideration should be made afresh in view of the teaching of the instant application without unwarranted reliance on isolated negative observations that, in themselves, provide merely eminently rebuttable evidence for the lack of enablement of a monomolecular antisense pharmaceutical.

Second, notwithstanding the lack of direct relevance of the cited references to the enablement of the instantly claimed dimeric antisense pharmaceuticals, Applicants maintain that the cited references fail to support lack of enablement of the claimed antisense pharmaceutical compositions. Indeed, Applicants can cite numerous instances of success with antisense oligonucleotides that have been shown to be effective in various *in vivo* therapeutic applications. For example, the success of anti-HIV antisense oligos is evident from the results of numerous *in vivo* antisense studies. An initial single dose phase one study of Applicant's anti-HIV antisense oligonucleotide (GEM®92), administered orally at three dose levels as well as by injection, showed excellent safety results and demonstrated effective oral delivery in humans of these 2nd generation antisense agents (see www.hybridon.com/drugdevelop; and Zheng (1999) Curr. Opin. Mol. Ther.1: 521-3). Furthermore, Applicants' note that their earlier-developed antisense treatment, GEM®91, which corresponds to a 25-mer phosphorothioate oligonucleotide that also targets HIV, significantly reduced viremia in HIV-positive patients treated for up to eight days. Although concerns regarding the uniform safety of GEM®91 and a number of other antisense therapeutics may hinder their approval by the FDA and further commercial development, they do not negate patentability for lack of enablement of all antisense technology, because the standards

applied for FDA approval are not those required for patentability. The Federal Circuit has specifically stated that "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled" (citing *Scott v. Finney*, 34 F.3d (Fed. Cir. 1994), at MPEP 2164.05). Accordingly, the conjectural concern over "non-antisense" side effects of some antisense oligonucleotides cited in the Office Action is not at all determinative to enablement of the instantly claimed invention.

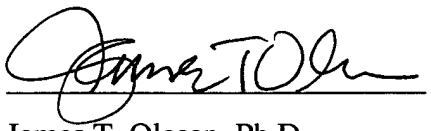
Indeed, there are many sequences known to be effective targets of antisense therapeutics. Much of the "unpredictability" cited in the Office Action pertains to target accessibility and other factors that have already been worked out in these numerous examples where an effective antisense therapeutic has been developed by elucidation of an appropriate region of the target mRNA for antisense binding. The broad negative statements quoted from Branch (1988) regarding "unexpected" effects on other targets and "in vivo....target site (inaccessibility)" are not relevant to the application of the instant invention to those targets that have already been proven amenable to effective antisense therapy. It is merely a matter of routine skill to adapt the dimeric antisense complexes of the instant invention to the elucidated effective target sequences previously developed using monomeric antisense compositions. Since Applicants could therefore cite numerous dimeric antisense compositions of the invention that would be pharmaceutically effective, the instantly claimed invention is enabled under 35 U.S.C. §112, first paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, 1st paragraph.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a Three (3) Month Extension of Time, and authorization of payment of the corresponding fee accompanies this Response. Please charge any additional fees or refund any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,



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